Rejection Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 44-56 under 35 U.S.C. § 112, first paragraph.

The Examiner stated that the specification teaches a method for preparing GD3 and GM2 ganglioside conjugate vaccines. The Examiner stated that the specification also teaches that immunization of mice with the GD3-Keyhole Limpet Hemocyanin (GD3-KLH) conjugate generated the highest titer of IgM and IgG responses compared to the other conjugates tested and that the sera was highly specific for GD3 in human tissue extracts. The Examiner stated that the specification teaches that melanoma patients immunized with the GM2-KLH generated high titers of IgM and IgG antibodies. The Examiner stated that the specification does not teach that the production of antibodies to GD3-KLH or GM2-KL results in the treatment of the cancer. The Examiner stated that the production of antibodies upon administration of a ganglioside conjugate vaccine cannot be extrapolated to the ability of the antibodies to prevent or treat cancer since in a previous study (Fung, et al.), no significant prolongation of survival was observed in mice that were administered a GM2-KLH conjugate vaccine, despite the ability of GM2-KLH to produce of high titers of anti-GM2 IgG antibodies. Therefore, the Examiner stated that the production of antibodies upon administration of a ganglioside conjugate vaccine is not sufficient to insure that these antibodies will also prevent or treat cancer.

In response, applicants respectfully traverse the Examiner's rejection based on the above-stated grounds. Applicants maintain that the claimed invention has been fully enabled by the disclosure of the application.

Specifically, applicants would like to point out that Fung, et al. should not be used to assess either the immunogenicity or

efficacy of ganglioside conjugate vaccines. Fung, et al. studied active specific immunotherapy of a murine mammary adenocarcinoma using a vaccine composed of the Thomsen Freidenreich hapten coupled to KLH and emulsified in Ribi adjuvant. See Fung, et al., Abstract, lines 3-5. A GM2-KLH conjugate vaccine served only as an experimental control using an unrelated hapten in order to exclude nonspecific effects. See Fung, et al., page 4310. There is no evidence presented in Fung, et al. to show that the studied cancer cells express GM2, nor is there evidence to show that GM2 antibodies were generated after vaccination. It is clear that the Fung, et al. experiments were not designed to evaluate either the immunogenicity or efficacy of a ganglioside conjugate vaccine.

The Examiner stated that the specification also does not provide guidance on the synthesis of conjugates with other gangliosides or chemically modified gangliosides. As described in the specification the ganglioside region of attachment to the carrier protein is important in maintaining the antigenicity of the ganglioside. The Examiner stated that due to the variations in both the carbohydrate and ceramide portions of various gangliosides, it is not clear if the method used to conjugate GD3 and GM2 to KLH could be applied to other gangliosides and still maintain the antigenicity of other gangliosides. The Examiner stated that the specification also does not provide guidance on the synthesis of derivatives of KLH not does the specification teach which derivatives would result in an enhanced antibody response.

In response, applicants maintain that enough guidance has been provided by the applicants' disclosure on the synthesis of conjugates with other gangliosides or chemically modified gangliosides, specifically the claimed gangliosides. Namely, the "[g]anglioside conjugation must be accomplished without altering the immune dominant carbohydrate moiety." See specification, page

32, lines 6-13. Applicants also provide specific procedures by which one skilled in the art could produce a conjugate comprising an immunogenic protein and a ganglioside that retains its structural integrity. See e.g. specification, Page 21, line 29-page 23, line 19; page 24, line 15-page 26, line 10; and page 43, line 26-page 50, line 11.

Regarding the Examiner's comments about the derivatives of KLH, applicants maintain the specification provides enabling teachings to generate such derivatives. Fragments of KLH may be generated by routine experiments such as limited proteolysis. Different modified forms of KLH may also be produced by routine experimentation. These derivatives may then be tested for their immunogenicity using the procedures disclosed in the specification. Only derivatives which are immunogenic will be selected. Accordingly, applicants maintain that the specification provides enough guidance to synthesize derivatives of KLH which would be effective in the subject vaccine.

In view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Rejection Under 35 U.S.C. §103

The Examiner stated that the claims 44-48, and 53-56 are rejected under 35 U.S.C. §103 as being unpatentable over Livingston, et al. (Cancer Res) in view of Ritter, et al. (1991) and Livingston, et al. (U.S. Pat. No. 5,102,663) and Ritter, et al. (1990).

The Examiner stated that Livingston, et al. teach a vaccine administered to melanoma patients for stimulating the production of antibodies directed against a carbohydrate epitope on the ganglioside, GM2. The Examiner stated that Livingston, et al. teach that the vaccine is administered at a concentrations of

100, 200, or 300 μg with an adjuvant, Bacillus Calmette-Guerin (BCG), and a pharmaceutically acceptable vehicle, phosphate buffered saline. The Examiner stated that Livingston, et al. teach that melanoma recurrence was delayed in patients developing GM2 antibodies after vaccination. The Examiner stated that Livingston, et al. teach that more patients produced IgM antibodies that IgG antibodies to the GM2. The Examiner stated that Livingston, et al. also teach the gangliosides GM2, GD2, and GD3 are expressed on the cell surface of human malignant melanomas. The Examiner stated that Livingston, et al. do not teach the conjugation of the GM2 vaccine with Keyhole Limpet Hemocyanin (KLH). The Examiner stated that Livingston, et al. also do not teach the use of any other gangliosides in a vaccine preparation.

The Examiner stated that Ritter, et al. (1991) teach that IgG responses to gangliosides may be increased by the covalent attachment of foreign carrier proteins such as KLH to the gangliosides resulting in the T cell help necessary for the response. The Examiner stated that Ritter, et al. discloses that the advantage of inducing an IgG antibody response (vs IgM) against gangliosides is that IgG a) has a higher affinity; b) is better able to penetrate solid tissues; c) is able to mediate antibody-dependent cell-mediated cytotoxicity; d) and is generally detectable in the serum for longer periods after immunization. The Examiner stated that Livingston, et al. (U.S. Pat. No. 5,102,663) teach that the gangliosides GM3, GM2, GD3, GD2, GT3, and O-acetyl GD3 are gangliosides that are prominent cell-membrane components of melanoma and other tumors of neuroectodermal origin. The Examiner stated that Ritter, et al. (1990) teach that GD3 derivatives such as GD3 lactone are more immunogenic that GD3.

The Examiner stated that it would have been obvious to one of ordinary skill in the art to modify the vaccine taught by

Livingston, et al. by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter, et al. (1991), thus providing the advantages taught above by Ritter, et al. (1991). The Examiner stated that it would have also have been obvious to substitute any of the gangliosides GM3, GD2, GD3, GT3 or O-acetyl GD3 for the GM2 ganglioside in the vaccine because they are all prominent cell-membrane components of melanoma as taught by Livingston, et al. (U.S. Pat 5,102,663) and one of ordinary skill in the art would expect that IgG antibodies against these gangliosides would react with the melanoma cells. It would also have been obvious to substitute GD3 lactone for the GM2 ganglioside in the vaccine because GD3 lactone is more immunogenic than GD3, as taught by Ritter, et al. (1990), and would be expected to produce and enhanced antibody response compared to GD3.

The Examiner stated that the optimization of the dosage, route of administration, and number of sites to administer the composition is within the skill of the ordinary artisan.

In response, applicants respectfully traverse the Examiner's §103 rejection. Claims 44, 46 and 47, which were amended in the December 10, 1996 Amendment, and claims 48-56 are directed to methods of using a ganglioside conjugate vaccine comprising a ganglioside conjugated to an immunogenic protein effective to stimulate or enhance antibody production in a subject, an effective amount of adjuvant and a pharmaceutically acceptable vehicle.

Livingston, et al. discuss immunizing melanoma patients with a vaccine composed of a ganglioside, GM2, mixed with adjuvant BCG. Conceded by the Examiner, Livingston, et al. do not disclose or teach a ganglioside conjugate vaccine, and therefore this article does not disclose or teach the claimed invention.

The applicants' claimed method of using a vaccine which comprises (1) a ganglioside conjugate which maintains the structural integrity of the oligosaccharide portion of the ganglioside, (2) an effective amount of adjuvant and (3) a pharmaceutically acceptable carrier. Ritter, et al. (1991) do not disclose or teach a ganglioside conjugate wherein the structural integrity of the oligosaccharide portion of the ganglioside remains intact. Ritter, et al. (1991) do not disclose or teach the use of adjuvants. As previously stated, applicants' specification clearly teaches the importance of maintaining the structural integrity of the oligosaccharide portion of the ganglioside and incorporating of an adjuvant in the claimed vaccine. Accordingly, Ritter, et al. (1991) do not disclose or teach the claimed invention.

Livingston, et al. (U.S. Patent 5,102,663) discuss a specific vaccine composed of only the 9-O-acetyl GD3 ganglioside and an adjuvant. Livingston, et al. never disclose nor teach conjugation of a ganglioside with any immunogenic protein.

Ritter, et al. (1990) disclose GD3 derivatives, specifically GD3 lactone, induced antibody responses in mice. Ritter, et al. do not suggest or motivate one skilled in the art to practice a ganglioside conjugate vaccine.

Even in combination, the cited references do not suggest or motivate a person of ordinary skill in the art to practice the subject invention. Regarding the Examiner's statement that "it would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston, et al. by conjugating the GM2 ganglioside to KLH, or to a derivative of KLH, because the conjugated vaccine would be expected to enhance the IgG response to the ganglioside, as taught by Ritter, et al. (1991)," applicants would like to point out that even assuming, arguendo, that an ordinary skilled artisan may be motivated to try to make

a useful ganglioside vaccine, there is no reasonable expectation of success for such attempt because as discussed hereinabove the structural integrity of the oligosaccharide portion of the ganglioside needs to be maintained during conjugation and an adjuvant needs to be included in the claimed vaccine. This guidance is only provided by the applicants' specification. Accordingly, applicants maintain that the combination of the cited references does not render the claimed invention obvious and respectfully request that the Examiner reconsider and withdraw the above ground of rejection.

The Examiner stated that claim 49 is rejected under 35 U.S.C. 103 as being unpatentable over Livingston, et al. (Cancer Res) in view of Ritter, et al. (1991) and Livingston, et al. (U.S. pat 5,102,663) and Ritter, et al. (1990) as applied to claims 44-48, and 53-56 above, and further in view of Kensil, et al. and Marciani, et al. The Examiner stated that the teachings of Livingston, et al. (Cancer Res) and Ritter, et al. (1991) and Livingston, et al. (U.S. Pat 5,102,663) and Ritter, et al. (1990) are set forth above. The Examiner stated that the above cited art does not teach the use of QS-21 as an adjuvant.

The Examiner stated that Kensil, et al. teach that QS-21 produced a higher antibody response that aluminum hydroxide. The Examiner stated that Kensil, et al. also teach that the immune responses obtained with QS-21 reached a plateau at doses between 10 and 80 μg in mice. The Examiner stated that Marciani, et al. teach the use of QS-21 as an adjuvant in a vaccine at concentrations of 10 and 20 μg. Marciani, et al. also teach that the QS-21 adjuvant did not cause a toxic reaction in cats.

The Examiner stated that it would have been obvious to one of ordinary skill in the art to add QS-21 as an adjuvant to the vaccine taught by the above cited art because QS-21 produces a higher antibody response than the commonly used adjuvant,

aluminum hydroxide, as taught by Kensil, et al., and QS-21 is not toxic to animals as taught by Marciani, et al. The Examiner stated that it would also have been obvious to use doses of between 10 and 200 μg because the immune response obtained with QS-21 plateaus at doses between 10 and 80 μg and optimization of the dose according to the subject receiving the vaccine is within the skill of the ordinary artisan.

In response, applicants respectfully traverse the Examiner's above rejection. Claims 44 and 46-56 are directed to a method of using a vaccine composed of a ganglioside conjugated to an immunogenic protein effective to stimulate or enhance antibody production in the subject, an effective amount of QS-21, and a pharmaceutically acceptable vehicle.

Applicants have already discussed Livingston, et al. (Cancer Res) and Ritter, et al. (1991) and Livingston, et al. (U.S. Patent 5,102.663) and Ritter, et al. (1990) hereinabove and would like to reiterate their prior position here. Kensil, et al. and Marciani, et al. teach uses of QS-21 as an adjuvant but they do not disclose ganglioside conjugate vaccines. As applicants have discussed hereinabove, none of the other references cited by the Examiner discloses, suggests or motivates an ordinary skilled artisan to make applicants' claimed invention. Even in combination, the cited references do not suggest or motivate a person of ordinary skill in the art to practice the subject invention. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the above §103 rejection.

The Examiner stated that claims 51 and 52 are rejected under 35 U.S.C. 103 as being unpatentable over Livingston, et al. (Cancer Res) in view of Ritter, et al. (1991) and Livingston, et al. (U.S. Pat 5,102,663) and Ritter, et al. (1990) as applied to claims 44-48, and 53-56 above, and further in view of Irie, et al.

The Examiner stated that the teachings of Livingston, et al. (Cancer Res) and Ritter, et al. (1991) and Livingston, et al. (U.S. pat 5,102,663) and Ritter, et al. (1990) are set forth above. The Examiner stated that it would have been obvious to one of ordinary skill in the art to modify the vaccine taught by Livingston, et al. by conjugating the GM2, or other gangliosides, to KLH for the reasons set forth above. The above cited art does not teach administration of the vaccine for treating cancer of epithelial origin or for producing antibodies to gangliosides found in the stroma of cancer.

The Examiner stated that Irie, et al. teach that the ganglioside GM2 is found on or in tumors of a variety of histological types including melanoma and breast carcinomas. The Examiner stated that it would have been obvious to one of ordinary skill in the art to administer the vaccine taught by the above cited art to patients afflicted with or susceptible to cancer of an epithelial origin (e.g. breast carcinomas) because the ganglioside GM2 is found in the stroma of the tumor as taught by Irie, et al. and one of ordinary skill in the art would expect that the antibodies produced by the vaccine react with the tumor and either treat or prevent the cancer.

In response, applicants respectfully traverse the above rejection. Claims 44, 46 and 47, which were amended in the December 10, 1996 Amendment, and claims 48-56 are directed to a method of using a ganglioside conjugate vaccine, wherein the gangliosides are found either in stroma of the cancer or the cancer is of epithelium or neuroectodermal origin.

Applicants have discussed Livingston, et al. (Cancer Res) and Ritter, et al. (1991) and Livingston, et al. (U.S. Patent 5,102.663) and Ritter, et al. (1990) hereinabove and would like to reiterate their prior position here. The fact that Irie, et al. teach that GM2 is found in several cancer types does not

disclose or teach the applicants' claimed invention. As applicants have discussed hereinabove, none of the other references cited by the Examiner discloses, suggests or motivates an ordinary skilled artisan to make applicants' claimed invention. Even in combination, the cited references do not suggest or motivate a person of ordinary skill in the art to practice the subject invention. Accordingly, in view of the foregoing, applicants respectfully request that the Examiner reconsider and withdraw the above §103 rejection.

In summary, for the reasons set forth hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds for objection and rejection set forth in the June 10, 1996 Office Action and earnestly solicit allowance of the claims now pending in the subject application, namely amended claims 44, 46 and 47, and claims 48-56.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee is deemed necessary in connection with the filing of this Supplemental Communication. However, if any other fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

Albert Wai Kit Chan

John P. White
Registration No. 28,678
Albert Wai-Kit Chan
Registration No. 36,479
Attorneys for Applicant(s)
Cooper & Dunham, LLP
1185 Avenue of the Americas
New York, New York 10036
(212) 278-0400